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Impact of Gene Polymorphisms, Platelet Reactivity, and the SYNTAX Score on 1-Year Clinical Outcomes in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

The GEPRESS Study

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the association between high on-treatment platelet reactivity (HPR) and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) for risk prediction of major adverse cardiovascular events (MACE) in patients with non–ST-segment elevation acute coronary syndrome (NSTEACS) undergoing percutaneous coronary intervention (PCI).

BACKGROUND Platelet function testing may be used to optimize antiplatelet therapy in high-risk patients, but identification of this category of patients remains challenging.

METHODS The GEPRESS (Gene Polymorphism, Platelet Reactivity, and the Syntax Score) study was a prospective, multicenter, observational study enrolling 1,053 patients with NSTEACS undergoing PCI and treated with clopidogrel. The platelet reactivity index (PRI) was measured at 3 time points: before PCI, at hospital discharge, and 1 month after PCI. Genetic variants of clopidogrel metabolism were determined in 750 patients. Patients were stratified by the presence of HPR (PRI >50%) and by tertile of the SS (upper SS tertile ≥15). The primary objective of this study was the risk of MACE in the period between 1 month and 1 year.

RESULTS Between 1 month and 1 year, 1-month HPR was an independent predictor of MACE in patients with an SS ≥15, but not in those with an SS <15, displaying a 5-fold increase in event rates (10.4% vs. 2.5%; $p < 0.0001$). CYP2C19*2 was the only single nucleotide polymorphism associated with HPR, but it was not associated with MACE. Although there was a significant variability in the PRI across the 1-month period, predischarge HPR and SS effectively stratified the risk of subsequent MACE up to 1-year follow-up.

CONCLUSIONS In clopidogrel-treated patients with NSTEACS undergoing PCI, HPR was independently associated with an increased risk of MACE only in the presence of a high SS. (J Am Coll Cardiol Intv 2014;7:1117–27) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CI = confidence interval

HPR = high on-treatment platelet reactivity

IDI = integrated discrimination improvement

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

NSTEACS = non-ST-segment elevation acute coronary syndromes

NSTEMI = non-ST-segment elevation myocardial infarction

OR = odds ratio

PRI = platelet reactivity index

ROC = receiver-operating characteristic

SNP = single nucleotide polymorphism

SS = SYNTAX score

VASP = vasodilator-stimulated phosphoprotein

High on-treatment platelet reactivity (HPR) has emerged as a risk factor for stent thrombosis and major adverse cardiovascular events (MACE) in patients who receive clopidogrel after percutaneous coronary intervention (PCI) (1). Multiple factors can contribute to these pharmacodynamic findings (2). In particular, genetic factors have been shown to be associated with poor responsiveness to clopidogrel (3), but their impact on the risk of MACE is controversial (4,5). Moreover, the low positive predictive value of HPR and the absence of large-scale randomized clinical trials supporting the use of platelet function testing question the utility of routine assessment of platelet reactivity in patients undergoing PCI (6). Accordingly, current guidelines do not endorse routine use of platelet function testing, but they suggest that in selected patients at high risk of a poor outcome after PCI, platelet function testing can be implemented to optimize antiplatelet therapy (7). However, identification of these patients remains challenging.

Prospectively developed for the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (8), the SYNTAX score (SS) has been shown to be associated with an increased risk of mortality, myocardial infarction (MI), and stent thrombosis in patients with non-ST-segment elevation acute coronary syndromes (NSTEACS) undergoing PCI (9). The relationship between the SS and the presence of HPR for the risk of MACE, however, has never been investigated. Other unsolved dilemmas include the relative prognostic value of platelet function testing versus pharmacogenetic information, the incremental prognostic value of the determination of platelet reactivity over time, and the existence of a therapeutic window for platelet reactivity. On this background, in the present study, we sought to investigate the following: 1) the association between platelet reactivity and the SS for the risk of MACE in patients with NSTEACS undergoing PCI treated with clopidogrel; 2) the association between genetic variants involved in clopidogrel-mediated platelet effects and the risk of MACE; 3) the incremental prognostic value of the platelet reactivity measured at several time points; and 4) the existence of a therapeutic window of platelet reactivity, which could be associated with a low risk of both ischemic and bleeding events.

METHODS

PATIENTS AND STUDY DESIGN. The GEPRESS (Gene Polymorphism, Platelet Reactivity, and the Syntax Score) study is a prospective, multicenter study designed to determine the impact of platelet reactivity, the SS, and the presence of several genetic variants modulating clopidogrel-mediated effects on the risk of ischemic and bleeding events in patients with NSTEACS undergoing PCI and treated with clopidogrel. Patients were eligible for enrollment if they had NSTEACS and at least 1 stenosis >50% requiring PCI. Patients were stratified by the presence of HPR and tertiles of the SS. HPR was defined using the vasodilator-stimulated phosphoprotein (VASP) assay as described in the following. SS was determined by experienced core angiographic laboratory technicians (Cardiovascular Research Foundation, New York, New York) blinded to clinical outcomes. For the purpose of the study, patients in the upper SS tertile (SS ≥15) were compared with patients in the mid or lower tertile (SS <15).

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Exclusion criteria were allergy or intolerance to aspirin and clopidogrel, need for concomitant oral anticoagulant therapy, cardiogenic shock, any contraindication or inability to comply with dual-antiplatelet therapy for 1 year, treatment with prasugrel or ticagrelor, and major comorbidities associated with life expectancy <1 year. The study was approved by the local ethics committee at each participating center, and all patients provided written informed consent.

PLATELET FUNCTION TESTING. Platelet reactivity was measured using the VASP assay (Biocytex, Marseille, France) using flow cytometric technique as previously described (10), and it was expressed as platelet reactivity index (PRI). HPR was defined as a PRI >50% as previously reported to be associated with ischemic recurrences and in agreement with expert consensus (11). The VASP assay was used to measure platelet reactivity because results are not affected by the use of glycoprotein IIb/IIIa inhibitors, which are commonly used in patients with NSTEACS, particularly among enrolling centers in this study. The PRI was determined at 3 time points: before PCI, at hospital discharge, and at 1 month after PCI. Clinical events were then correlated with the closest PRI determination performed before the event, so that periprocedural events were correlated with the PRI measured before PCI, events between discharge and 1 month with the PRI measured at hospital discharge, and events between 1 month and 1 year with the PRI determined at 1 month.

OBJECTIVE AND DEFINITIONS. The primary objective of this study was to investigate the association between 1-month HPR and the SS for the risk of MACE (cardiac mortality, MI, and stent thrombosis) in the period between 1 month and 1 year. The rationale for considering 1-month HPR was that previous investigations have shown that in clopidogrel-treated patients undergoing PCI, platelet reactivity improves over the course of the first week of treatment and HPR rates may be spuriously high if determined too early (12). Secondary endpoints included all-cause death, cardiac death, MI, cardiac death/MI, stent thrombosis, and bleeding determined in the periprocedural period, between hospital discharge and 1 month, and between 1 month and 1 year. The impact of genetic variants of clopidogrel metabolism on the risk of MACE was determined as well. NSTEACS included unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI). Unstable angina was defined as the presence of typical chest pain at rest with an electrocardiographic documentation of ischemia, whereas NSTEMI was defined as the presence of typical chest pain associated with an increase of troponin levels. Stent thrombosis was defined according to the Academic Research Consortium definition (13). Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definition (14). Net adverse clinical events were defined as the occurrence of MACE and BARC bleeding. The other definitions of the study are reported in Online Table 1.

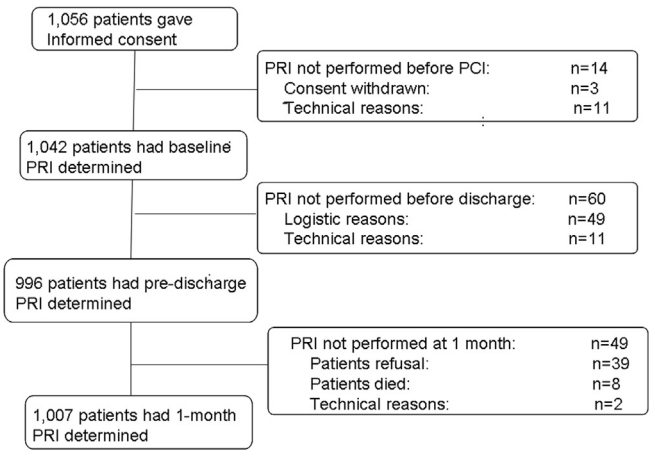

FIGURE 1 Flow Diagram of the Study

Platelet reactivity index (PRI) was determined before percutaneous coronary intervention (PCI), at hospital discharge, and 1 month after PCI.

PERCUTANEOUS CORONARY INTERVENTION. PCI was performed according to the standard of care. The choice of anticoagulant (unfractionated heparin, low molecular weight heparin, bivalirudin), use of glycoprotein IIb/IIIa inhibitors, as well as the type of stent was left to the operator's discretion. All patients were treated with 250 mg aspirin at clinical presentation. Patients who were not receiving long-term clopidogrel therapy (≥7 days) at the time of PCI were treated with a 300-mg or 600-mg clopidogrel loading dose. After PCI, patients were treated with aspirin 160 mg/day indefinitely, and clopidogrel 75 mg/day was recommended for 1 year.

GENOTYPIC ANALYSIS. A total of 14 single nucleotide polymorphisms (SNPs) potentially implicated in modulating clopidogrel-mediated effects were determined. DNA was extracted from whole blood by an automated purification system (MagCore HF16, RBC Bioscience Corp., Taiwan). The MassARRAY Assay Design 4.0 software (Sequenom, Inc., San Diego, California) was used to design 2 multiplex polymerase chain reactions for the SNP analysis. Genotyping

TABLE 1 Clinical Characteristics of Patients Included in the Study

Variable	Whole Cohort	Genetic Cohort	p Value
Age, yrs	67 (58–77)	67 (58–77)	0.57
Male	76.1 (803/1,056)	75.3 (565/750)	0.77
Body mass index, kg/m^2	26.6 (24–29)	28.0 (24–30)	0.02
Hypercholesterolemia	56.7 (598/1,056)	58.8 (441/750)	0.38
Hypertension	72.0 (760/1,056)	72.4 (543/750)	0.88
Smoking	49.8 (525/1,056)	52.9 (397/750)	0.19
History of coronary artery disease	30.2 (319/1,056)	31.6 (237/750)	0.56
Diabetes mellitus	26.8 (283/1,056)	27.9 (209/750)	0.65
Peripheral vascular disease	8.0 (84/1,056)	9.1 (68/750)	0.45
Renal dysfunction	11.7 (123/1,056)	12.9 (97/750)	0.45
Chronic obstructive pulmonary disease	9.7 (102/1,056)	10.1 (76/750)	0.80
Unstable angina, %	39.5 (417/1,056)	36.4 (273/750)	0.20
NSTEMI	60.5 (639/1,056)	63.6 (477/750)	0.20
Previous myocardial infarction	24.8 (262/1,056)	28.8 (216/750)	0.07
Previous PCI	23.6 (249/1,056)	25.5 (191/750)	0.39
Previous CABG	7.1 (75/1,056)	8.0 (60/750)	0.53
Left ventricular ejection fraction	55.0 (48–60)	51.2 (48–60)	0.65
Preprocedural clopidogrel treatment			
Chronic therapy*	9.0 (74/822)	10.0 (51/508)	0.59
Bolus 300 mg ≤1 h before PCI	21.9 (180/822)	27.8 (141/508)	0.02
Bolus 300 mg >1 h before PCI	29.6 (243/822)	29.5 (150/508)	0.99
Time from bolus to PCI, h	25.0 (16.0–48.0)	35.5 (22.0–49.5)	
Bolus 600 mg ≤1 h before PCI	18.4 (151/822)	24.2 (123/508)	0.01
Bolus 600 mg >1 h before PCI	11.1 (91/822)	2.2 (11/508)	<0.001
Time from bolus to PCI, h	12.0 (4.0–18.0)	24.0 (8.0–48.0)	
Long-term therapy or 600 mg bolus >12 h	13.4 (110/822)	11.4 (58/508)	0.34
Therapy at discharge			
Aspirin	99.2 (1,048/1,056)	99.6 (747/750)	0.51
Clopidogrel	99.7 (1,053/1,056)	100 (750/750)	0.38
Beta-blocker	78.7 (830/1,056)	78.1 (586/750)	0.86
ACEI	73.2 (772/1,056)	54.0 (570/750)	0.18
Statin	86.7 (915/1,056)	60.5 (638/750)	0.38
Nitroderivate	16.9 (178/1,056)	11.5 (121/750)	0.73
Calcium channel blocker	11.9 (126/1,056)	9.2 (97/750)	0.57
Angiotensin receptors blocker	10.5 (111/1,056)	7.4 (78/750)	0.99
Diuretic agent	16.9 (178/1,056)	13.8 (146/750)	0.17
Proton pump inhibitor	53.4 (563/1,056)	54.2 (407/750)	0.73
Ranitidine	33.2 (350/1,056)	31.8 (239/750)	0.60

Values are median (interquartile range) or % (n/N). *Clopidogrel treatment for at least 7 days before the procedure.

ACEI = angiotensin-converting enzyme inhibitor; CABG = coronary artery bypass graft; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

was performed using iPLEX Gold technology, as previously described (15), and MassARRAY high-throughput DNA analysis with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, according to manufacturer's instructions. Hardy-Weinberg equilibrium was tested in all patients included in the genetic study. Participation in the genetic substudy of the GEPRESS trial was voluntary for sites and patients. Collection and genetic analysis of samples was subject to informed consent from all patients and to approval by the local ethics committee. The consent was separate from that of the main study.

SAMPLE SIZE AND STATISTICAL ANALYSIS. As the relationship between the PRI and the SS for the risk of MACE has never been investigated, to determine the sample size of the study, we based our assumptions on the association between PRI and the risk of MACE. Assuming an area under the receiver-operating characteristic (ROC) curve of 0.65, with a null hypothesis set at 0.50, $\alpha = 0.05$, $\beta = 0.10$, and an incidence of MACE of 5% between 1 month and 1 year, a sample of 840 patients would be required to show an association between PRI and MACE. Considering a patient drop-out rate of 10%, we aimed to recruit ~1,000 patients. Continuous data are presented as median and interquartile range and were compared by the Kruskal-Wallis 1-way analysis of variance. The Dunn test was used to determine significant differences for multiple comparisons. Categorical variables were compared by the chi-square or Fisher exact test, as appropriate. Time-to-event outcomes were analyzed by Kaplan-Meier analysis, and differences were compared using the log-rank test. ROC curves were generated to determine the discriminative power of the PRI and the SS for the risk of ischemic and bleeding events. The optimal cutoff point was calculated by determining the value with the greatest sum of sensitivity and specificity. Stepwise multivariable Cox regression analyses were performed to assess independent predictors of MACE between 1 month and 1 year. Several multivariable models were constructed to determine the additive prognostic value of the PRI and the SS after adjusting for main confounders known to have an impact on the risk of MACE, as suggested by previous studies (16,17). The prognostic accuracy of each model was assessed by the C-statistic, the integrated discrimination improvement (IDI), and the net reclassification improvement (18,19). The following variables were included in the stepwise multivariable models: clinical presentation with NSTEMI (positive troponin levels), PRI, SS, renal dysfunction, age, and diabetes. The same analyses were repeated in the cohort of patients who had the left ventricular ejection fraction (LVEF) determined or who underwent the genetic screening for loss-of-function or gain-of-function alleles involved in clopidogrel absorption or metabolism. SNPs were tested for their association with HPR by logistic regression analysis using a stepwise multivariable model after adjusting for clinical characteristics. Other variables included in the model were age, sex, diabetes, smoking, renal dysfunction, therapy with proton pump inhibitors, body mass

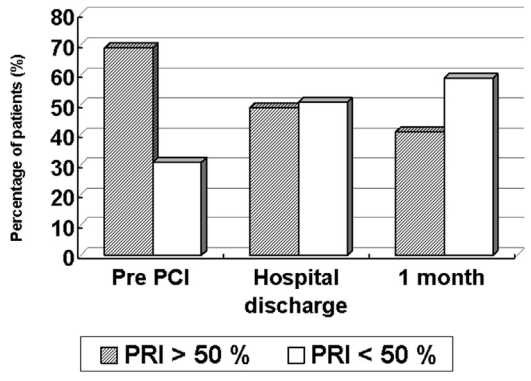

FIGURE 2 Proportion of Patients With a PRI >50% Measured Before PCI, at Hospital Discharge, and 1 Month After PCI

The proportion of patients with PRI>50% was 69% before PCI, 49% at hospital discharge, and 41% 1 month after PCI. Abbreviations as in Table 1.

index, NSTEMI at hospital admission, LVEF, number of vessel disease, and the SS. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 12.0, software (SPSS, Inc., Chicago, Illinois). Values $p < 0.05$ were considered statistically significant.

RESULTS

STUDY POPULATION. The flow diagram of the study is shown in Figure 1. A total of 1,056 NSTEACS patients provided written informed consent; 3 patients withdrew consent before hospital discharge, and therefore 1,053 patients were finally included in the study. Follow-up rates were 100% at 30 days and 99% at 1 year. All patients were compliant with dual-antiplatelet therapy at 30 days, whereas 5 patients interrupted clopidogrel between 1 month and 1 year (2 patients for personal decision and 3 because of unplanned noncardiac surgery). These patients were excluded from the landmark analysis between 30 days and 1 year. Clinical and angiographic characteristics of patients included in the study are shown in Table 1 and Online Table 2, respectively. A total of 366 patients were in the lower SS tertile (SS ≤8), 309 in the intermediate tertile (8<SS<15), and 365 in the upper tertile (SS ≥15).

GENOTYPIC AND PHENOTYPIC ANALYSIS. PRI values significantly changed from baseline to 1-month follow up ($p < 0.001$). Median (interquartile range) PRI values were 63% (44% to 76%) at baseline, 50% (34% to 66%) at hospital discharge, and 46% (32% to 60%) at 1 month ($p < 0.05$ for all comparisons). As shown

TABLE 2 Association Between Genetic Variants Modulating Clopidogrel-Mediated Effects and Platelet Reactivity Index Determined at 1 Month

SNP	Patients	PRI, %	p Value	PRI >50%	p Value
CYP2C19*2, 681 G>A			<0.001		<0.001
GG	69.2 (496/717)	44 (30-59)		39.3 (195/496)	
GA	27.9 (200/717)	52 (40-65)		56.0 (112/200)	
AA	2.9 (21/717)	66 (54-73)		81.0 (16/21)	
CYP2C19*3, 636 G>A			0.12		0.39
GG	99.7 (715/717)	47 (32-61)		44.9 (321/715)	
GA	0.3 (2/717)	NA		100 (2/2)	
AA	0.0 (0/717)	NA		NA	
CYP2C19*4, 1 A>G			0.50		0.62
AA	99.0 (710/717)	48 (32-61)		45.2 (321/710)	
GA	1.0 (7/717)	41 (24-59)		28.6 (2/7)	
GG	0.0 (0/717)	NA		NA	
CYP2C19*17, 806 C>T			0.04		0.16
CC	63.7 (456/716)	49 (34-62)		47.4 (216/456)	
TC	33.2 (238/716)	46 (32-60)		41.6 (99/238)	
TT	3.1 (22/716)	35 (17-55)		31.8 (7/22)	
CYP3A4*1G, intron 10C>T			0.44		0.87
CC	76.4 (548/717)	48 (32-62)		45.4 (249/548)	
TC	22.5 (161/717)	46 (31-60)		43.5 (70/161)	
TT	1.1 (8/717)	51% (49-67)		50.0 (4/8)	
CYP3A4*1B, 3924 A>G			0.72		0.67
AA	93.2 (668/717)	48 (32-61)		44.8 (299/668)	
GA	6.8 (49/717)	48 (31-64)		49.0 (24/49)	
GG	0.0% (0/717)	NA		NA	
CYP3A5*3, 6986 G>A			0.47		0.98
GG	85.9 (616/717)	48 (32-61)		45.0 (277/616)	
GA	13.8 (99/717)	48 (34-62)		45.5 (45/99)	
AA	0.3 (2/717)	NA		50.0 (1/2)	
ABCB1, 3435 C>T			0.08		0.08
CC	26.4 (189/716)	42 (31-61)		43.9 (83/189)	
TC	52.7 (377/716)	47 (32-60)		42.7 (161/377)	
TT	20.9 (150/716)	51 (37-62)		53.3 (80/150)	
IRS-1, 227497991 A>G			0.11		0.33
AA	90.5 (649/717)	47 (32-61)		44.3 (288/649)	
AG	9.4 (67/717)	51 (40-63)		50.7 (34/67)	
GG	0.1 (1/717)	NA		100 (1/1)	
IRS-1, 227382808 G>C			0.78		0.28
GG	80.5 (575/714)	48 (32-61)		46.2 (266/575)	
GC	17.9 (128/714)	46 (34-59)		39.1 (50/128)	
CC	1.5 (11/714)	47 (38-56)		36.4 (4/11)	
PON1, 163 A>T			0.21		0.34
AA	39.2 (281/717)	49 (34-61)		48.0 (135/281)	
TA	45.3 (325/717)	46 (30-61)		42.2 (137/325)	
TT	15.5 (111/717)	48 (33-62)		45.9 (51/111)	
PON1, 575 A>G			0.72		0.46
AA	47.8 (343/717)	47 (32-60)		42.9 (147/343)	
GA	43.1 (309/717)	48 (32-62)		47.6 (147/309)	
GG	9.1 (65/717)	48 (31-60)		43.1 (28/65)	
ITGB3, 196 T>C			0.76		0.78
TT	67 (479/717)	47 (32-61)		44 (211/479)	
TC	31 (224/717)	49 (32-61)		46 (104/224)	
CC	2 (14/717)	50 (36-63)		50 (7/14)	

Values are % (n/N) or median (interquartile range).
NA = not available; PRI = platelet reactivity index; SNP = single nucleotide polymorphism.

TABLE 3 Clinical Outcomes of Patients Stratified by the PRI

	PRI >50%	PRI ≤50%	p Value
Clinical outcomes between PCI and hospital discharge (stratified by pre-procedural PRI)*			
MACE‡	3.1 (22)	3.4 (11)	0.91
Death	0.0 (0)	0.0 (0)	NA
Cardiac death	0.0 (0)	0.0 (0)	NA
Cardiac death/myocardial infarction	2.9 (21)	3.4 (11)	0.81
Myocardial infarction	2.9 (21)	3.4 (11)	0.81
Stent thrombosis	0.1 (1)	0.3 (1)	0.86
Any BARC bleeding	0.3 (2)	0.3 (2)	0.59
BARC ≥2	0.0 (0)	0.0 (1)	0.68
Clinical outcomes between discharge and 30 days (stratified by PRI at hospital discharge)*			
MACE	1.2 (6)	0.8 (4)	0.71
Death	0.6 (3)	0.9 (5)	0.76
Cardiac death	0.6 (3)	0.4 (2)	0.97
Cardiac death/myocardial infarction	1.0 (5)	0.8 (4)	0.96
Myocardial infarction	0.8 (4)	0.4 (2)	0.65
Stent thrombosis	0.8 (4)	0.0 (0)	0.13
Any BARC bleeding	0.4 (2)	1.2 (6)	0.31
BARC ≥2	0.0 (0)	0.4 (2)	0.49
Clinical outcomes between discharge and 1 year (stratified by PRI at hospital discharge)†			
MACE	5.6 (28)	2.0 (10)	0.002
Death	3.3 (16)	2.4 (17)	0.93
Cardiac death	2.3 (11)	0.8 (5)	0.11
Cardiac death/myocardial infarction	5.8 (28)	2.0 (10)	0.002
Myocardial infarction	4.1 (20)	1.0 (5)	0.002
Stent thrombosis	1.9 (9)	0.2 (1)	0.01
Any BARC bleeding	3.1 (16)	5.0 (25)	0.18
BARC ≥2	1.1 (5)	3.7 (18)	0.007
Clinical outcomes between 1 month and 1 yr (stratified by 30-day PRI)†			
MACE	5.6 (23)	1.6 (9)	0.0003
Death	3.2 (13)	1.9 (12)	0.27
Cardiac death	2.2 (9)	0.5 (3)	0.02
Cardiac death/myocardial infarction	5.6 (23)	1.4 (8)	0.002
Myocardial infarction	3.7 (15)	0.9 (5)	0.002
Stent thrombosis	1.2 (5)	0.2 (1)	0.03
Any BARC bleeding	1.7 (7)	4.5 (26)	0.02
BARC ≥2	0.3 (1)	3.5 (20)	0.0006

Values are % (n). *p values determined by chi-square statistic. †Estimates of risk are determined by Kaplan-Meier analyses and compared with the log-rank test. ‡Includes cardiac death, myocardial infarction, and stent thrombosis.

BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular events; other abbreviations as in Tables 1 and 2.

in Figure 2, the percentage of patients with HPR was 69% before PCI, 49% at hospital discharge, and 41% at 1 month. The association between genetic variants modulating clopidogrel effects and 1-month PRI values is shown in Table 2. All SNPs tested in the region of interest were in Hardy-Weinberg equilibrium ($p > 0.05$) except for CYP2C19*5. Among the SNPs tested, only CYP2C19*2 was significantly associated with HPR. Independent predictors of HPR at 1 month were CYP2C19*2 (odds ratio [OR]: 2.16, 95% confidence interval [CI]: 1.56 to 3.00; $p < 0.0001$), diabetes mellitus (OR: 1.41, 95% CI: 1.01 to 1.99; $p = 0.045$), and smoking (OR: 0.68, 95% CI: 0.50 to 0.93; $p = 0.01$). Therapy with proton pump inhibitors had borderline statistical significance (OR: 1.32, 95% CI: 0.97 to 1.78; $p = 0.07$).

CLINICAL OUTCOMES. Clinical outcomes stratified by HPR are shown in Table 3. Of note, no association was apparent between the presence of preprocedural HPR and the risk of periprocedural MACE or between HPR at hospital discharge and the risk of MACE between hospital discharge and 30-day follow up. In contrast, in the period between 1 month and 1 year, patients with either HPR at 1 month (Figure 3A), or with an SS ≥15 (Figure 3B) had significantly higher rates of MACE compared with patients without HPR or an SS <15, respectively. Moreover, as shown in Table 3, patients without HPR had significantly higher rates of bleeding than patients with HPR. There was no significant difference between the discriminatory power of PRI measured at 1 month compared with PRI measured at hospital discharge for events occurring between 1 month and 1 year, although C-statistic values were slightly better for PRI measured at 1 month both for MACE (C-statistic, 0.63 vs. 0.60, respectively; $p = 0.61$) and bleeding (C-statistic, 0.73 vs. 0.66, respectively; $p = 0.23$). Clinical outcomes stratified by HPR and the SS are shown in Table 4. As shown in Figure 3C, in the period between 1 month and 1 year, the risk of MACE was 10.4% in patients with HPR and an SS ≥15 and 2.5% in those with HPR but an SS <15 ($p < 0.0001$). Similarly, patients with HPR at hospital discharge and an SS ≥15 displayed the highest risk of MACE, cardiac mortality, MI, and stent thrombosis in the period between hospital discharge and 1 year compared with other patients. Of note, no association was apparent between the risk of MACE at any time point and CYP2C19*2 (Online Table 3).

MULTIVARIABLE ANALYSES. Multivariable analyses with or without HPR and the SS are shown in Table 5 (models 1 through 4). Age and diabetes mellitus were the only clinical variables associated with an increased risk of MACE in the period between 1 month and 1 year (model 1). The effect size of HPR and the SS are shown in models 2 and 3. As shown in model 4, after adjusting for age and diabetes mellitus, the association between HPR and an SS ≥15 (OR: 12.2, 95% CI: 3.5 to 42.7), but not between HPR and an SS <15 (OR: 3.33, 95% CI: 0.82 to 13.53) was an independent predictor of MACE. Similarly, HPR was an independent predictor of MACE in patients with an SS ≥15 (OR: 3.78, 95% CI: 1.03 to 13.83, $p = 0.04$), but not

in those with an SS <15 (OR: 2.91, 95% CI: 0.70 to 11.92, p = 0.14). However, no significant interaction was apparent between the 2 variables (p = 0.87). Performance measures in models with or without HPR and the SS are shown in Online Table 4. Including HPR (model 2) improved the prognostic performance of the multivariable models with only age and diabetes mellitus (model 1), but the model including both HPR and the SS (model 3) had the best prognostication performances, with a C-statistic of 0.81, a net reclassification improvement of 18%, and an IDI of 2.3% compared with the model including age, diabetes mellitus, and HPR (model 2). Results did not significantly change when we considered the cohort of patients who had an LVEF or the genotype determined. There was no independent relationship between any SNPs and the risk of MACE.

THERAPEUTIC WINDOW. The optimal cutoff values determined by ROC analyses for the risk of MACE (PRI >51%) or BARC bleeding ≥2 (PRI ≤40%) in the period between 1 month and 1 year were used to stratify patients into 3 groups: group 1 had a PRI ≤40%, group 2 had a PRI between 40% and 51%, and group 3 had a PRI >51%. As shown in **Figure 4**, the incidence of net adverse clinical events was 5.8% in group 1, 3.2% in group 2, and 6.2% in group 3 (p = 0.37).

DISCUSSION

This is the first study investigating the relative impact of HPR, SS, and genetic variants modulating clopidogrel effects on the risk of MACE in patients with NSTEACS undergoing PCI. The main findings of this study are as follows: 1) after adjusting for main confounders, HPR determined at 1 month was associated with significantly higher rates of MACE between 1 month and 1 year in patients in the upper SS tertile, but not in those in the intermediate or lower tertile; 2) although CYP2C19*2 was the only SNP associated with HPR, it was not independently associated with the risk of MACE; 3) although platelet reactivity significantly varied across the 1-month period, there was no significant difference between PRI measured at 1 month and PRI measured at hospital discharge for risk prediction of both ischemic and bleeding events in the period between 1 month and 1 year; and 4) a therapeutic window of PRI in the 40% to 51% range defined a group of patients with a trend toward a lower risk of net clinical outcome.

Several observational studies have consistently reported an association between HPR and the risk of stent thrombosis and MACE (1,20), suggesting

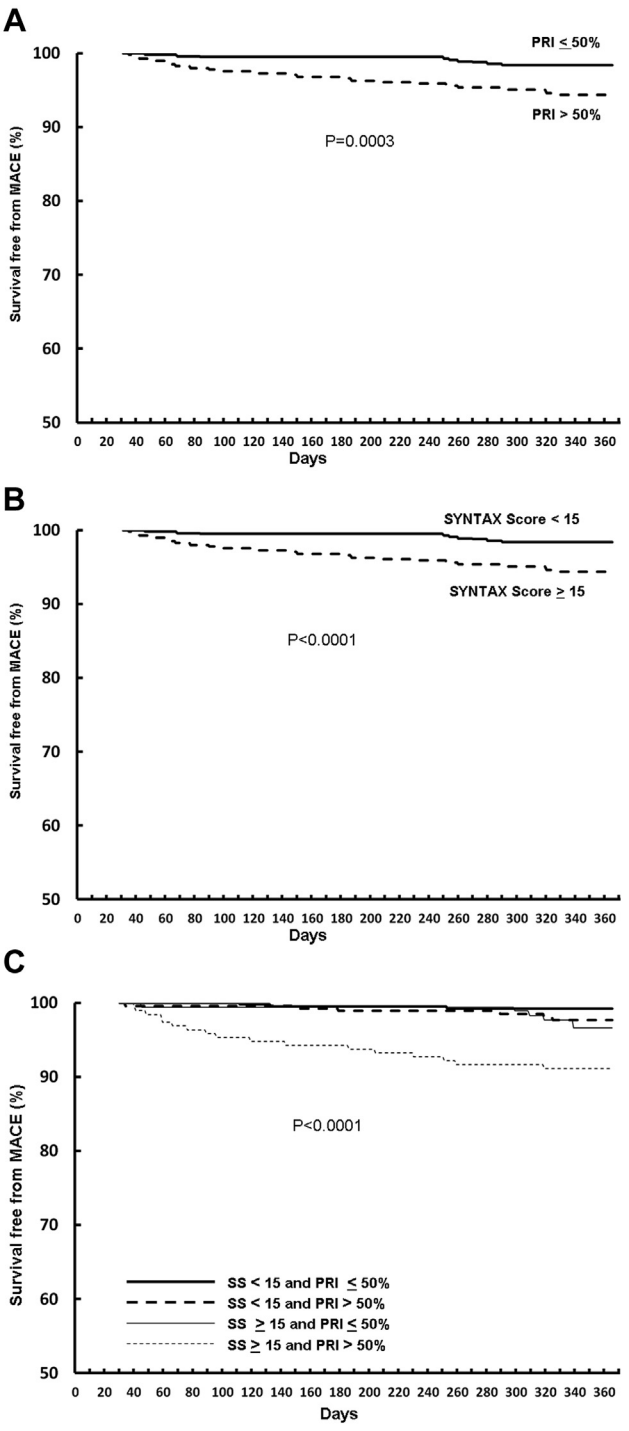

FIGURE 3 Kaplan-Meier Analysis Showing Survival Free From Major Adverse Cardiac Events

Survival free from major adverse cardiac events (MACE) in patients stratified by the platelet reactivity index (PRI) **(A)**, the SYNTAX score (SS) **(B)**, and both PRI and SS **(C)**. Patients were stratified by tertiles of SS, and then the upper tertile of SS (≥15) was compared with pooled mid and lower SS tertiles.

TABLE 4 Clinical Outcomes Stratified by PRI Values and the SS

	PRI >50%, SS ≥15	PRI >50%, SS <15	PRI ≤50%, SS <15	PRI ≤50%, SS ≥15	p Value
Periprocedural outcomes (stratified by pre-procedural PRI)*					
MACE	3.9 (10)	2.4 (11)	4.3 (9)	1.9 (2)	0.42
Death	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NA
Cardiac death	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NA
Cardiac death/myocardial infarction	3.9 (10)	2.4 (11)	4.3 (9)	1.9 (2)	0.42
Myocardial infarction	3.9 (10)	2.4 (11)	4.3 (9)	1.9 (2)	0.42
Stent thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	NA
Any BARC bleeding	0.8 (2)	0.0 (0)	0.0 (0)	1.9 (2)	0.02
BARC ≥2	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.04
Outcomes between hospital discharge and 30 days (stratified by PRI at hospital discharge)*					
MACE	2.5 (5)	0.0 (0)	0.8 (3)	0.7 (1)	0.04
Death	1.5 (3)	0.0 (0)	1.1 (4)	0.7 (1)	0.26
Cardiac death	1.5 (3)	0.0 (0)	0.3 (1)	0.7 (1)	0.11
Cardiac death/myocardial infarction	2.5 (5)	0.0 (0)	0.8 (3)	0.7 (1)	0.04
Myocardial infarction	2.0 (4)	0.0 (0)	0.6 (2)	0.0 (0)	0.03
Stent thrombosis	2.0 (4)	0.0 (0)	0.0 (0)	0.0 (0)	0.001
Any BARC bleeding	0.0 (0)	0.7 (2)	1.4 (5)	0.7 (1)	0.36
BARC ≥2	0.0 (0)	0.0 (0)	0.6 (2)	0.0 (0)	0.32
Outcomes between hospital discharge and 1 year (stratified by PRI at hospital discharge)†					
MACE	10.8 (22)	2.1 (6)	1.7 (6)	2.8 (4)	<0.0001
Death	6.6 (13)	1.1 (3)	2.2 (9)	5.6 (8)	0.003
Cardiac death	4.1 (8)	1.1 (3)	0.6 (2)	1.4 (3)	0.01
Cardiac death/myocardial infarction	11.3 (22)	2.1 (6)	1.7 (6)	2.8 (4)	<0.0001
Myocardial infarction	8.8 (17)	1.1 (3)	1.1 (4)	0.7 (1)	<0.0001
Stent thrombosis	4.2 (8)	0.4 (1)	0.0 (0)	0.7 (1)	<0.0001
Any BARC bleeding	3.2 (6)	3.2 (10)	5.3 (19)	4.2 (6)	0.55
BARC ≥2	1.1 (2)	1.1 (3)	3.7 (13)	3.5 (5)	0.07
Outcomes between 30 days and 1 yr (stratified by 30-day PRI)†					
MACE	10.4 (17)	2.5 (6)	0.8 (3)	3.4 (6)	<0.0001
Death	4.5 (8)	2.1 (5)	0.7 (3)	4.9 (9)	0.005
Cardiac death	3.7 (6)	1.2 (3)	0.3 (1)	1.1 (2)	0.02
Cardiac death/myocardial infarction	10.4 (17)	2.5 (6)	0.8 (3)	2.8 (5)	<0.001
Myocardial infarction	7.5 (12)	1.3 (3)	0.5 (2)	1.7 (3)	<0.001
Stent thrombosis	2.5 (4)	0.4 (1)	0.0 (0)	0.6 (1)	0.02
Any BARC bleeding	1.9 (3)	1.7 (4)	4.5 (18)	4.5 (8)	0.14
BARC ≥2	0.0 (0)	0.4 (1)	3.3 (13)	4.0 (7)	0.008

Values are % (n). *p Values are determined by chi-square statistic. †Estimates of risk are determined by Kaplan-Meier analyses and are compared with the log rank test.
SS = SYNTAX score; other abbreviations as in Tables 2 and 3.

that platelet function testing could be used to optimize antiplatelet therapy on the basis of platelet responsiveness to clopidogrel. However, no such evidence has been provided so far by large-scale interventional studies, which failed to demonstrate the utility of platelet function testing to guide antiplatelet therapy after PCI (6). Accordingly, guidelines do not endorse the routine use of platelet function testing, with the possible exception of high-risk patients who are expected to have a poor outcome after PCI (7). However, identifying this category of patients remains challenging.

The GEPRESS study is the first to identify a subset of patients in whom platelet function testing may provide incremental prognostic value. Patients with HPR and a high SS displayed a 5-fold higher risk of MACE compared with patients with HPR and a low SS, and in the multivariable analysis, HPR was independently associated with increased rates of MACE in patients in the upper tertile of SS, but not in those in the intermediate or lower tertiles. Moreover, adding the SS in the multivariable model, which already included conventional risk factors and HPR, was associated with a net

TABLE 5 Independent Predictors of MACE in the Period Between 1 Month and 1 Year Including or Not the PRI Determined at 1 Month and the SS

	OR (95% CI)	p Value
Model 1		
Age	1.06 (1.02–1.09)	0.001
Diabetes	2.59 (1.27–5.30)	0.009
Model 2		
Age	1.06 (1.02–1.09)	0.001
Diabetes	2.52 (1.23–5.19)	0.01
PRI >50%	3.55 (1.61–7.83)	0.002
Model 3		
Age	1.04 (1.02–1.08)	0.004
Diabetes	2.37 (1.14–4.93)	0.02
PRI >50%	3.05 (1.37–6.80)	0.006
SS ≥15	3.78 (1.69–8.42)	0.002
Model 4		
Age	1.04 (1.02–1.08)	0.004
Diabetes	2.37 (1.14–4.93)	0.02
SS ≥15 and PRI >50%*	12.20 (3.48–42.66)	<0.0001
SS ≥15 and PRI ≤50%	4.21 (1.03–17.16)	0.045
SS <15 and PRI >50%	3.33 (0.82–13.53)	0.10

*The reference group is represented by patients with a PRI ≤50% and SS <15.
CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1, 3, and 4.

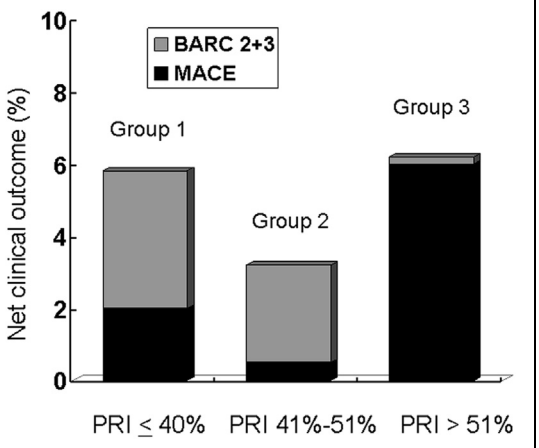

FIGURE 4 Net Clinical Outcome Including Ischemic and Bleeding Events in Patients Stratified According to Clopidogrel Responsiveness

A therapeutic window of PRI was identified that defined patients at lower risk of both ischemic and bleeding events. MACE includes cardiac mortality, myocardial infarction, and stent thrombosis. BARC = Bleeding Academic Research Consortium; other abbreviations as in Table 3.

reclassification improvement of 18% and an IDI of 2.3%.

Finding a trade-off between the risk of ischemic and bleeding events is a key determinant for improving the benefit of antiplatelet therapy. Importantly, our study shows a nonlinear relationship between platelet reactivity and the risk of ischemic and bleeding events, suggesting that, below specific thresholds of PRI, ischemic events are not further reduced (PRI <51%), whereas the risk of bleeding is increased (PRI <40%). In view of the limitations of currently available antiplatelet treatments, fine titration of the antiplatelet therapy with a consistent effect within a specific therapeutic window might therefore reveal a better strategy to optimize the outcomes of patients with NSTEACS undergoing PCI. These findings are consistent with those of previous studies that identified a therapeutic window for platelet reactivity using a different assay, which defined a group of patients with a balanced risk of ischemic and bleeding events (12).

Also consistent with other studies (12), we observed a significant variability in platelet responsiveness to clopidogrel across the 1-month period. However, there was no significant difference between PRI measured at 1 month and PRI measured at hospital discharge for risk prediction of both MACE and bleeding occurring between 1 month and 1 year. Moreover, HPR and SS at hospital discharge effectively stratified the subsequent risk of MACE up to 1-year follow-up. Therefore, notwithstanding the variability in platelet reactivity across the 1-month period in patients with NSTACS, our findings suggest that risk stratification can be effectively performed also at hospital discharge using pre-discharge PRI and the SS.

These observations from the GEPRESS study may be important for the use of the more potent $P2Y_{12}$ receptor inhibitors. In fact, although both prasugrel and ticagrelor significantly reduce the risk of ischemic events compared with clopidogrel (21,22), they are associated with an increased risk of major bleeding. Moreover, the results of our study showing that HPR was a predictor of adverse outcomes only among patients with an SS ≥15 may explain why previous trials of tailoring antiplatelet therapies that stratified patients only based on HPR did not yield clinical benefit. Indeed, our study findings may set the basis for the design of future randomized trials of tailored antiplatelet therapy with more potent $P2Y_{12}$ receptor inhibitors.

Some studies have reported an association between genetic variants associated with the clopidogrel metabolic pathway and the risk of MACE in patients undergoing PCI (5), but others have refuted this association (4). In the GEPRESS study, only CYP2C19*2 was independently associated with HPR, but it was not associated with an increased risk of

MACE at any time point. Our study, therefore, does not support the concept of individualizing antiplatelet therapy on the basis of pharmacogenetic information. This may be explained by the fact that CYP2C19*2 accounts for only 5% to 12% of the inter-individual variability of response to clopidogrel (23), which is affected by several other clinical and demographic variables. Although this study may be underpowered to find a link between genetic testing and poor outcomes, it suggests that platelet function testing may be more sensitive than genetic testing in predicting the risk of MACE. Platelet function testing in fact is sensitive to more variables affecting the response to clopidogrel, and therefore it is closer to the phenotypic characteristics of the patients.

STUDY LIMITATIONS. The impact of genetic variants on the risk of MACE was performed in a subgroup of patients (n = 750), and therefore it may be underpowered. Lacking external validation, the range of PRI values suggested to minimize the risk of ischemic and bleeding events should be interpreted with caution. Troponin levels were determined at each interventional site, and therefore some variability between different assays may exist. Subgroup analyses were not performed due to insufficient statistical power. The test for interaction between HPR and SS was not statistically significant. However, the study did not have sufficient statistical power to detect such an interaction.

CONCLUSIONS

HPR is associated with increased rates of ischemic events only in patients with a high SS, suggesting a possible setting in which platelet function testing could be implemented to optimize antiplatelet therapy. CYP2C19*2 was the only genetic variant significantly associated with HPR, but it was not associated with the risk of MACE.

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KEY WORDS clopidogrel, platelet reactivity, SYNTAX score

APPENDIX For supplemental tables and a figure, please see the online version of this article.